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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The mechanisms of free radical oxidation of organic compounds have been studied. It has been determined that unsaturated peroxy radicals will undergo cyclization reactions leading to a variety of cyclic peroxide compounds. It appears that peroxy radicals derived from natura-ly occurring organic compounds such as rubbers, fats, and oils, are converted into a variety of compounds that contain the cyclic peroxide nucleus. Simple model compounds that permit the study of the peroxy radical cyclization have been examined.

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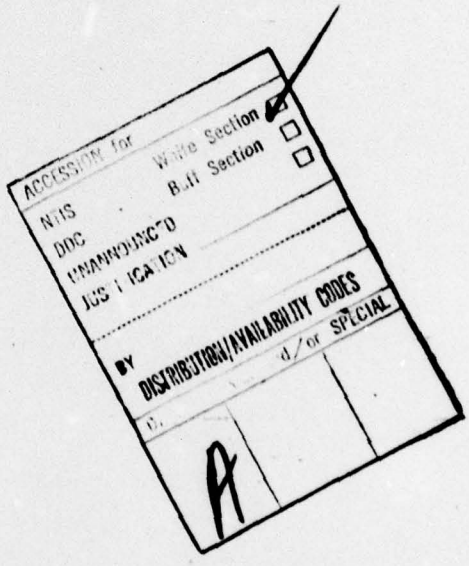
These model studies show that, in addition to cyclic peroxides, a variety of compounds that include epoxides and alcohols are formed by free radical mechanisms. Thus, primary products to be expected from autoxidation of natural materials such as fats and rubbers are mono and bicyclic peroxides and epoxy alcohols.



The destruction of organic substrates by molecular oxygen is perhaps one of the most important organic reactions. Natural and synthetic polymers, biological materials such as lipids, and for that matter, any organic molecule exposed to the atmosphere may react with ground state molecular oxygen. It is no surprise then, that extensive investigations have focused on the kinetics of organic substrate oxidation by O_2.[1] The "hydroperoxide mechanism" for autoxidation which is now generally accepted is outlined below:

1. $R\text{-}H + I\cdot \longrightarrow R\cdot + H\text{-}I$ Initiation

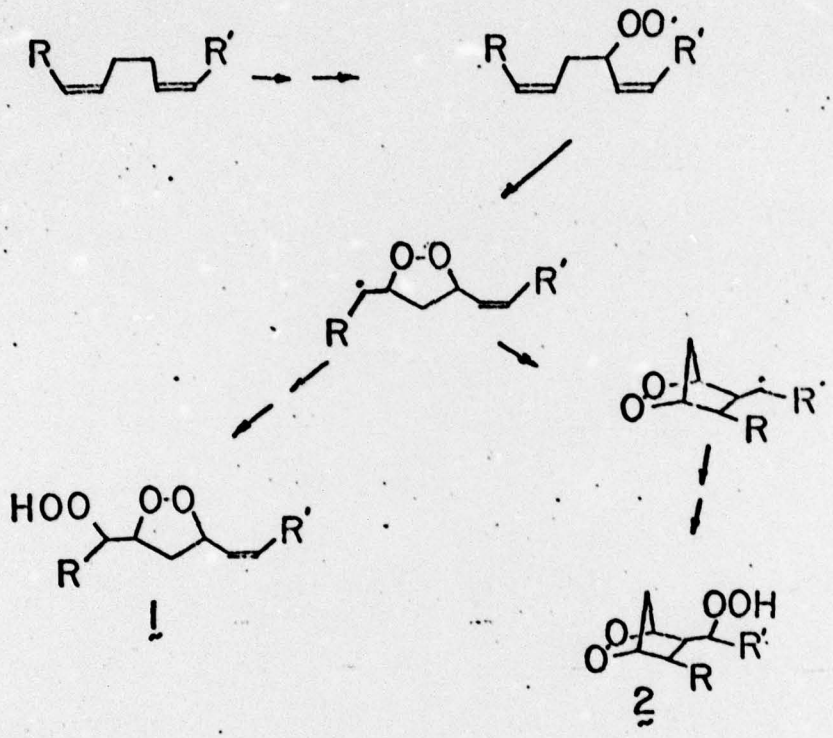
2. $R\cdot + O_2 \longrightarrow RO\text{-}O\cdot$ } Propagation

3. $RO\text{-}O\cdot + R\text{-}H \longrightarrow ROOH + R\cdot$ }

4. Termination

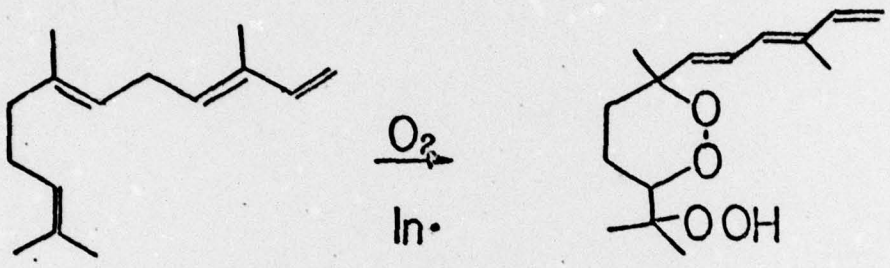
Despite the numerous studies on autoxidation and inhibition, surprisingly little research has been directed towards product study in autoxidation. It is true that for simple molecules like isopropylbenzene[2] the primary autoxidation product is the tertiary hydroperoxide. However, if the organic substrate has several centers of unsaturation, the simple hydroperoxide product may not be found and in its place, cyclic peroxides are formed. For example, squalene[3] absorbs two moles of oxygen upon autoxidation and

one of these oxygen molecules is incorporated as a peroxide, rather than a hydroperoxide group. Although no rigorous structure proof was offered for the squalene oxidation product, it seems likely on the basis of subsequent work[4] that the principal product of squalene autoxidation is one of the cyclic peroxides (1 or 2) formed by the mechanism described below:



In this mechanism, the first formed peroxy radical can undergo cyclization to give either a moncyclic peroxide 1 or the bicyclic species 2. Peroxy radical cyclization, then, probably plays an important role in determining the products of squalene autoxidation.

Another example of peroxy radical cyclization is provided by the work of Anet et. al.[5] who found the monocyclic peroxide 3 as the primary product of autoxidation of α-farnesene. Peroxy radical cyclization is again implicated in this example of autoxidation and thus cyclic peroxides must be considered as potential primary autoxidation products of polyunsaturated materials such as natural and synthetic rubbers and other commercially important polymers.



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It should also be noted that bicyclic endoperoxides like 2 have been shown to be intermediates in prostaglandin biosynthesis and two classes of prostaglandin, PGG and PGH, have the bicyclic endoperoxide functionality incorporated in their structure.[6,7] The chemistry of monocyclic and bicyclic endoperoxides is thus of interest with reference to uncontrolled autoxidation of naturally occuring compunds as well as in the enzymatically controlled oxidation of polyunsaturated fatty acids. Very little is known however, about the chemistry of mono and bicyclic endoperoxides like 1 and 2 since compounds of this type have not been synthetically available. Recently, however, we[8,9] and others[10] have

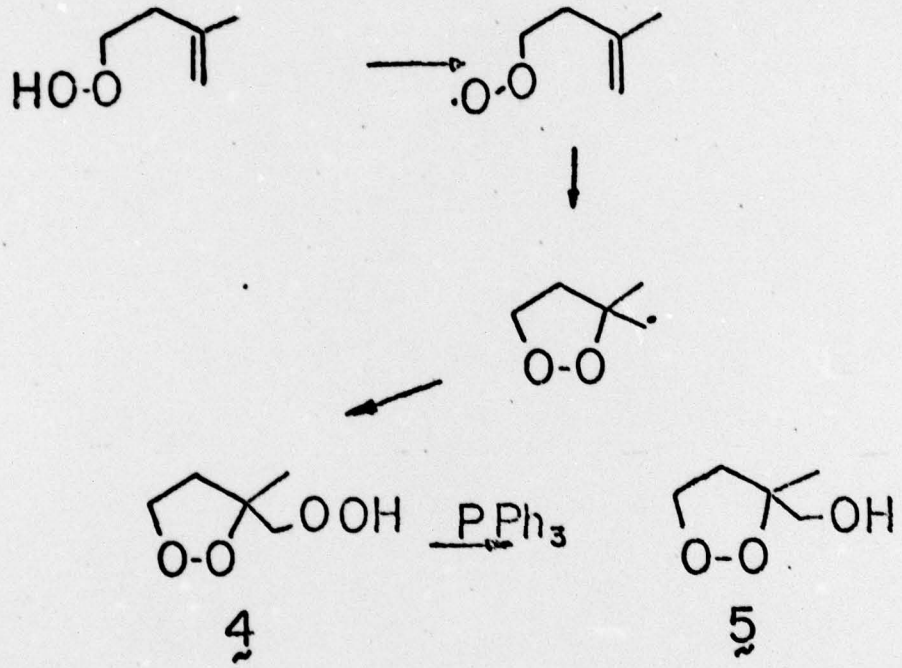
developed synthetic methods that readily provide compunds like 1 and 2 along with a variety of analogs.

B. The Synthesis of Cyclic Peroxides

1. *Radical Cyclization*

We have developed a general method for the synthesis of cyclic peroxides based on the free radical cyclization of unsaturated hydroperoxides[4,8]. The method is described in Figure 1 and proceeds by an intermediate peroxy radical, generated from the corresponding hydroperoxide.

Figure 1.



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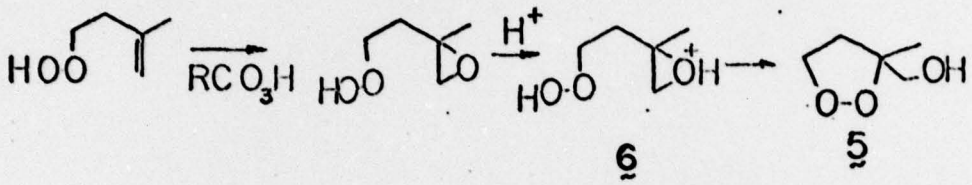
The hydroperoxide 4 and the alcohol 5 are available from this reaction scheme as are several other five and six membered ring analogs. Systematic investigation has shown that the ease of cyclization is (in the terminology proposed by Baldwin[11]) 5 ring exocyclic (as in Fig. 1) > 6 ring exo > 7 ring exo > endocyclic cyclization.[4]

2. *Ionic cyclization*

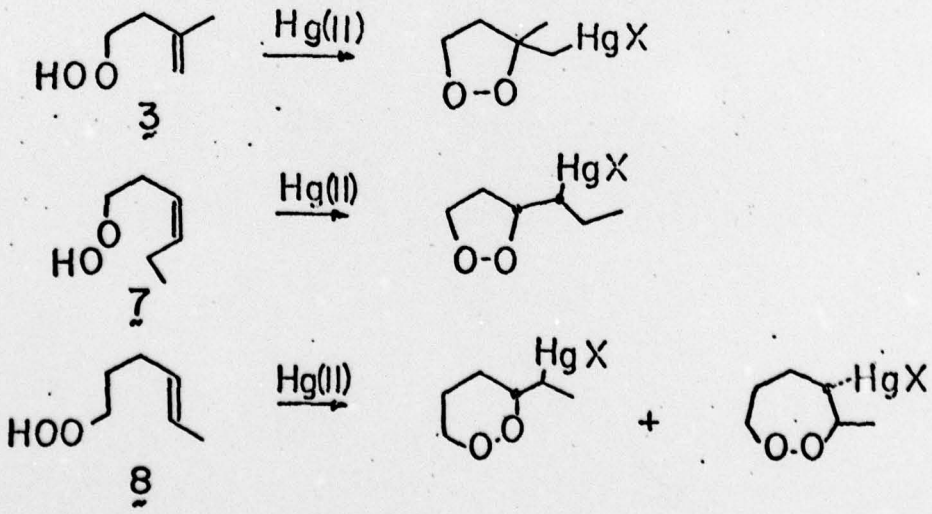
The cyclic peroxide 5 and a variety of analogs can be prepared by the acid catalyzed cyclization of oxirane hydroperoxides.[4] This cyclization has also been systematically studied and five and six membered ring analogs



6 5

of 5 are readily available. The cyclization presumably proceeds via nucleophilic attack of the hydroperoxide on the protonated epoxide 6 and this suggested that cyclization might also be affected by other electrophilic reagents acting directly on the starting unsaturated hydroperoxide.

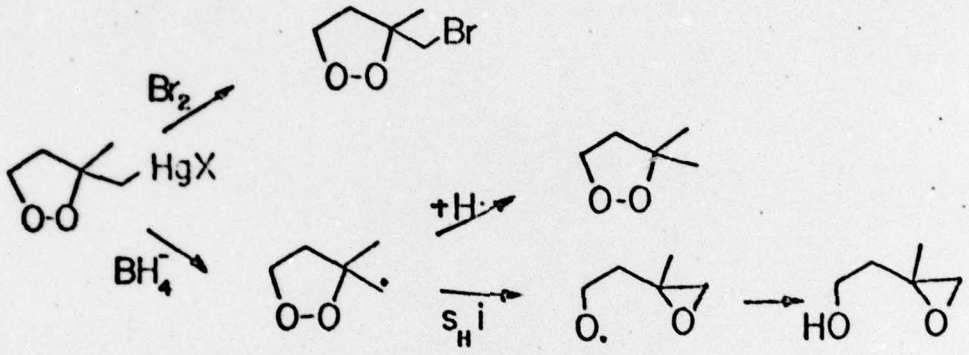
Reaction of the unsaturated hydroperoxide with mercuric nitrate[12] leads to the cyclic peroxides shown below. Yields are excellent (80-90%) and the compounds (as the bromides) can be purified by high pressure liquid chromatography (HPLC). Five membered ring exocyclic cyclization is exclusive for cyclizations of 3 and 7, and 8 leads to a mixture of six membered exocyclic and seven



membered endocyclic products that are separated by HPLC.

All of the peroxymercuric compounds can be readily converted to the β-bromoperoxides by reaction with bromine (Fig. 2).[13]

Borohydride reduction leads to saturated cyclic peroxides and ring cleavage products, oxirane alcohols. The reduction of alkylmercuric compounds by BH_4^- proceeds via a radical mechanism[14] and the mechanism of epoxide formation is shown below in Figure 2.



β-Alkyl radical attack on the peroxide linkage leads to the formation of the epoxide and the alkoxy radical. This radical attack on the peroxide linkage has ample precedent in the studies of the "unzipping" of styrene-oxygen copolymer[13,15] and the reaction can be categorized as an intramolecular example of an S_H2 reaction (commonly referred to as S_Hi).

The research supported by DAH CO 4-75-G-0117 has been a blend of mechanistic and synthetic peroxide chemistry. We have studied peroxy radical cyclizations mechanistically, and we have prepared the compounds that are favored from these cyclization reactions by independent synthetic routes.

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